SPATIAL CORRESPONDENCE BASED ASYMMETRY ANALYSIS IN FMRI

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ABSTRACT

Asymmetry analysis of brain activation in functional magnetic resonance imaging (fMRI) experiments is commonly used to determine hemispheric specialization for cognitive function. Asymmetry is typically expressed in terms of differences in the number of suprathreshold voxels activated, normalized to total activation, within specific regions known to subserve the function of interest or over the entire hemisphere. We introduce methodologies for carrying out asymmetry analysis both for region of interest (ROI) and whole brain based studies that take into account information about spatial correspondence of voxels on two sides of the brain. We apply this methodology to make determination of activation asymmetry during a memory encoding task in patients with refractory temporal lobe epilepsy (TLE). Memory lateralization is an important step in the presurgical evaluation of such patients for temporal lobectomy. Using *structure specific* analysis, our asymmetry scores in hippocampus are found to have a strong correspondence with hemispheric dominance given by Intracortical Amobarbital Testing (IAT), which is the widely accepted *gold standard* for determining laterality. Whole brain analysis, on the other hand, is used to locate regions in the brain with asymmetric activation in an exploratory analysis. These methods of quantifying asymmetry using spatial correspondence have the potential for generating more robust asymmetry measurements.

***Index Terms*—** fMRI, asymmetry, epilepsy, memory, IAT, Wada

1. INTRODUCTION

ROI based analysis of fMRI data provides increased power for testing structure-specific hypotheses as compared to voxel based approaches. However, heterogeneity of brain function within ROI can undermine the sensitivity of this approach for detecting meaningful effects. The availability of a common shape based coordinate system within a predefined ROI provides a natural point-by-point correspondence that can provide a local measure of asymmetric activation at each point of the ROI.

In this paper, we make use of continuous medial representation (cmrep) [1] based shape modeling for functional asymmetry analysis within the hippocampus, a critical region for memory function. This provides an *asymmetry map* over the entire volumetric ROI that can be informative about the variability of asymmetric activation within different subregions. Asymmetry indices generated by integrating such maps may provide a more powerful statistical measure than conventional voxel count based indices. We also extend this concept of utilizing spatial correspondence information in measuring functional asymmetry to whole brain fMRI analysis. A symmetric whole brain template is constructed for this purpose [2, 3] and the individual functional data are mapped to this template. Whole brain asymmetry maps can be generated in the template space and regions showing asymmetric activation can be identified.

Lateralization of language function has been reliably performed using fMRI [4]. However, use of fMRI for memory lateralization hasn't been shown to be as reliable, despite a lot of promise as potentially being a noninvasive alternative to IAT [5]. In section 3, we show that correspondence based measures of asymmetry in hippocampus as introduced here has a strong concordance with hemispheric dominance as reported by IAT in a cohort of TLE patients. Other regions in the temporal lobe, including parahippocampal gyrus, are identified in whole brain asymmetry maps as being predictive of IAT lateralization.

2. MATERIALS AND METHODS

2.1. Functional Imaging

The memory encoding task consisted of viewing of complex visual scenes in a blocked design experiment with alternating blocks of scene encoding or control. Subjects were instructed to remember the scenes for a subsequent recognition task. Passive viewing of randomly scrambled scene was used as control condition. Bold fMRI images were obtained from a 3 Tesla Siemens Trio scanner, using a gradient echo echo-

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planar (EPI) sequence with TR = 3000ms, TE = 30 ms, and 3 mm isotropic voxels. A high resolution (voxel size 0.9375 x 0.9375 x 1.5 mm) T1-weighted structural MRI scan was also obtained. Further details of the experimental protocol can be found in [6]. 20 patients with TLE participated in the study, out of which 12 had their IAT dichotomized according to hemispheric dominance for memory for comparison with fMRI data.

The EPI data were motion corrected, aligned to the structural image and smoothed with an isotropic Gaussian kernel (6 mm FWHM). A general linear model (GLM) was used to generate activation maps that measure the correlation between smoothed EPI timeseries and a boxcar task function convolved with a canonical model of the hemodynamic response function using Statistical Parametric Mapping software [7]. The resulting contrast images were used for both whole brain and ROI based analysis as described below.

2.2. Region of Interest Analysis

We use the structure-specific fMRI analysis framework described in [8]. Each subject's hippocampi are segmented by an expert. The deformable cm-rep model [1] was fitted to each hippocampus. The model imposes a 3D coordinate system on the interior of the structure of interest, hippocampus in this case. On the one hand, this provides a consistent set of coordinates between left and right hippocampi in the same subject as well as across subjects, thus making spatial correspondence information available. On the other hand, because the axes are based on the medial geometry of hippocampus, location of a point along the axes naturally annotates different subregions and its position relative to the shape of the structure. While two coordinate axes describe location on the medial surface, the third describes the relative position of a point between the boundary and the medial axis. For example, if z denotes the coordinate along the long axis on the medial surface of the hippocampus, $z = 0$ represents a point near the head and $z = 1$ represents one near the tail of the hippocampus. Let $\mathbf{x}$ be the location of a point in the cmrep coordinate system and $C_L(\mathbf{x})$ and $C_R(\mathbf{x})$ be the fMRI contrast images mapped to $\mathbf{x}$ for left and right hippocampus respectively. An asymmetry map over the ROI can be computed as $A(\mathbf{x}) = (C_L(\mathbf{x}) - C_R(\mathbf{x}))/(|C_L(\mathbf{x})| + |C_R(\mathbf{x})|)$. Examples of asymmetry maps are shown in Figure 1. We define the asymmetry index over the whole ROI as

$$AI = \frac{1}{V}\int_{\mathbf{x}\in\Omega} \frac{C_L(\mathbf{x}) - C_R(\mathbf{x})}{|C_L(\mathbf{x})| + |C_R(\mathbf{x})|} dV, \qquad (1)$$

where dV is the volume element at the cmrep coordinate $\mathbf{x}$, V is the volume of the ROI and Ω is the cmrep domain. Conventionally, asymmetry index is calculated as $(N_L - N_R)/(N_L + N_R)$ where N_L and N_R are the number of suprathreshold voxels in the statistical parametric map within the hand-drawn ROIs in the left and right hemispheres respectively. This measure is sensitive to the threshold chosen, and since the information about the distribution of the locations of suprathreshold voxels within the ROI is not used, we do not know if one subregion has more asymmetric activation than another. For comparison, we also calculated asymmetry index as $(M_L - M_R)/(|M_L| + |M_R|)$, where M_L and M_R are mean contrast images over the hand-drawn left and right ROI respectively.

One way analysis of variance is conducted to determine if asymmetry index as calculated from fMRI is predictive of memory lateralization as given by IAT. Results are discussed in section 3.

2.3. Whole Brain Analysis

In order to study asymmetric activation over the whole brain, we have to establish point correspondence between the two hemispheres. For this purpose, we construct a symmetric anatomical template. Similar techniques have been used for fMRI [9]. However, we use a cohort-specific template based on symmetric shape averaging that can improve performance [2]. The (non-symmetric) template is flipped about the mid sagittal plane and a *shape and appearance* based mean of the two images is defined as the image that requires minimal total deformation to be diffeomorphically registered to the two input images. This mean image is used as the symmetric template. Our approach differs from existing approaches [9, 10] where the symmetric template is only an *appearance* based average of the original and flipped template images – thus, shape differences may still exist between homologous structures in the left and right hemispheres.

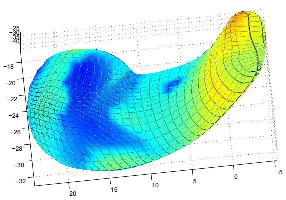
The individual subject brains as well as their contrast images are mapped to this symmetric template. Whole brain asymmetry maps are generated by reflecting the contrast images $C(\mathbf{x})$ ($\mathbf{x}$ being the 3D voxel location) about the mid-sagittal plane in the template space. Let $C'(\mathbf{x})$ be the reflected contrast image. Asymmetry map over the whole brain is then given by $A(\mathbf{x}) = (C(\mathbf{x}) - C'(\mathbf{x}))/(|C(\mathbf{x})| + |C'(\mathbf{x})|)$.

Once voxelwise asymmetry maps are available in the template space, a two sample t-test is performed at every voxel between patient subgroups classified by IAT as left and right memory dominant. Significant clusters found by this analysis may point to regions where functional asymmetry is correlated with memory lateralization.

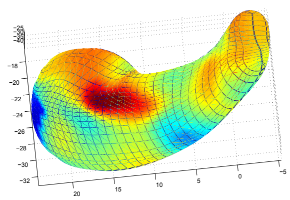
3. RESULTS

Figure 1 shows results of ROI based asymmetry analysis using the cmrep model. Panels (a) and (b) show fMRI task contrasts for a subject rendered on the surface of the cmrep model of the hippocampus for the left and right ROI respectively. We can observe that while the right ROI seems to have more task related activation overall, different subregions have different levels of *relative activation*. Normalization to a shape based coordinate system allows us to capture the spatial variation of asymmetric activation over the ROI. This can be seen in the asymmetry maps in panels (c) and (d). Note that the asymmetry map in panel (c) is derived from a subject with right lateralized IAT memory score, while that in panel (d) is that of a left lateralized one. Despite the spatial variations in the respective asymmetry maps, the difference in overall asymmetry consistent with the IAT laterality can be clearly observed.

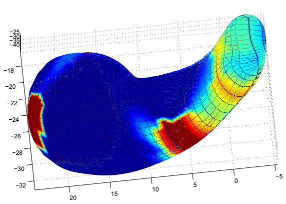
Asymmetry index for each subject is computed using equation 1. Asymmetry indices are also computed using conventional method [6] as well as mean contrast. Figure 2 shows the difference in asymmetry indices for subjects with left and right-lateralized IAT. IAT laterality is more strongly correlated with spatial correspondence based asymmetry indices with a clear separation between the two groups.



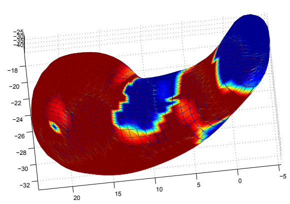
(a) Left Contrast



(b) Right Contrast



(c) Asymmetry map for a right lateralized subject



(d) Asymmetry map for a left lateralized subject

Fig. 1. All panels show maximum intensity projection of quantities of interest inside the hippocampus computed in the cmrep coordinate system. (a) and (b) show fMRI task contrast maps in the left and right hippocampus of a subject (blue is less contrast, red is more). (c) and (d) show asymmetry maps for two subjects with right and left lateralized memory functions in IAT respectively. Blue means more activation in the right, red means more activation in the left.

Functional asymmetry in hippocampus has been shown to be correlated with IAT laterality using ROI analysis. Exploratory analysis of asymmetry map over the whole brain, on the other hand, can reveal other regions that may be informative of memory lateralization. Table 1 lists significant clusters that are found to be correlated with IAT laterality. Interestingly, two of the largest clusters found are in the parahippocampal area which is sometimes included as part of a larger

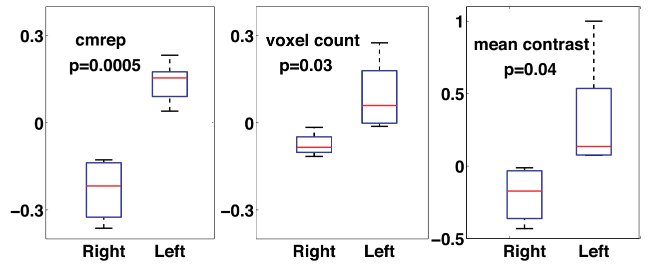


Fig. 2. Box plots showing asymmetry indices of patients with left and right dominant IAT memory laterality. Asymmetry indices are computed using cmrep (left), voxel count (middle) and mean contrast over the ROI. Group separation is much more significant using cmrep (p=0.0005) than using conventional voxel count (p=0.03) as well as mean contrast based (p=0.04) asymmetry analysis.

#	max T	Size	MNI Coord	BA	AAL
1	8.66	134	-17 -26 -21	30	ParaHippocampal L
2	14.58	127	-17 -36 -8	27	ParaHippocampal L
3	10.27	114	-13 53 0	10	Frontal Sup Medial L
4	17.57	113	-23 -61 -11	19	Lingual L
5	9.34	102	-52 -25 25	48	SupraMarginal L

Table 1. Table showing clusters of voxels where asymmetry scores are significantly different between patients with left and right lateralized memory scores in IAT. Each cluster is labeled by Brodmann area (BA) and Anatomic Area Labels (AAL). A minimum cluster size of 100 and an uncorrected threshold of $p < 0.001$ were used.

ROI for classical asymmetry analysis for presurgical memory lateralization in TLE patients [6] (also see Figure 3). A cluster is also found in Brodmann area 48, which is part of the hippocampus. Some other clusters found by this analysis may be artifactual. Even though we use an optimal symmetric template, some misalignment of smaller structures is difficult to avoid, lessening the power of statistical tests, particularly with a small sized dataset such as ours. Nonetheless, the appearance of clusters in the parahippocampal and hippocampal areas is encouraging and is consistent with the memory lateralization literature [6]. Note that since the analysis is being done on a symmetric template, it suffices to report clusters on either hemisphere. A left hemispheric mask was used, hence all the areas reported are in the left side of the brain.

4. DISCUSSION

We have introduced methods for functional asymmetry analysis both in the whole brain and in structures of interest that make use of spatial correspondence of voxels. Structure specific analysis uses normalization of data to a shape based co-

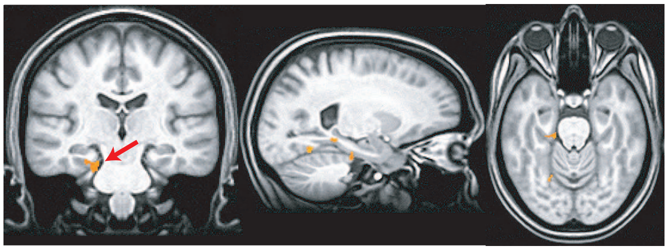


Fig. 3. Areas where asymmetry scores of patients with left and right dominant memory in IAT differ significantly. The arrow points to a region in the parahippocampal area. Clusters in red are overlaid on the symmetric whole brain template and shown only in the left hemisphere.

ordinate system, whereas whole brain study normalizes data to a symmetric template generated by deformable registration based tools. This allows for the construction of both structure specific and whole brain functional asymmetry maps. These can help visualize regional differences in functional asymmetry and can be integrated to generate summary statistics.

We have shown these spatial correspondence based asymmetry measures to be useful for presurgical memory lateralization in TLE patients. Our results suggest that the ROI and whole brain based approaches can be complementary to each other for functional asymmetry analysis. While certain subcortical structures like the hippocampus are difficult to align in whole brain normalization, thus necessitating ROI based analysis as we have done here, other structures that may have significant asymmetric activation can be found by whole brain analysis which might otherwise be missed. In the application presented here, for example, the parahippocampal gyrus shows a strong asymmetric activation concordant with IAT lateralization in whole brain analysis, which can in turn serve as motivation for doing structure-specific analysis in this area. This has the potential for further improving the reliability and power of asymmetry analysis, hopefully taking us closer to be able to use fMRI as a noninvasive alternative to IAT.

Ongoing work will validate these methodologies on a larger dataset of patients and include structure specific analysis on ROIs such as the parahippocampal gyrus revealed by whole brain analysis. The asymmetry scores will also be regressed against neuropsychological measures to assess their value for predicting surgical outcome. One could also further extend the idea of using correspondence in the time domain. Instead of using contrast images as produced by a GLM, one could directly compare the activity of corresponding voxels at the *same* time points.

5. REFERENCES

[1] Paul A. Yushkevich, Hui Zhang, and James C. Gee, "Continuous medial representation for anatomical structures.," *IEEE Trans Med Imaging*, vol. 25, no. 12, pp. 1547–64, 12 2006.

[2] B.B. Avants, C.L. Epstein, and J.C. Gee, "Symmetric shape averaging in the diffeomorphic space," *Biomedical Imaging: From Nano to Macro, 2007. ISBI 2007. 4th IEEE International Symposium on*, pp. 636–639, 12-15 April 2007.

[3] B. B. Avants, C. L. Epstein, M. Grossman, and J. C. Gee, "Symmetric diffeomorphic image registration with cross-correlation: Evaluating automated labeling of elderly and neurodegenerative brain.," *Med Image Anal*, 6 2007.

[4] J. R. Binder, S. J. Swanson, T. A. Hammeke, G. L. Morris, W. M. Mueller, M. Fischer, S. Benbadis, J. A. Frost, S. M. Rao, and V. M. Haughton, "Determination of language dominance using functional MRI: a comparison with the Wada test.," *Neurology*, vol. 46, no. 4, pp. 978–84, 4 1996.

[5] H. W. Robert Powell and John S. Duncan, "Functional magnetic resonance imaging for assessment of language and memory in clinical practice.," *Curr Opin Neurol*, vol. 18, no. 2, pp. 161–6, 4 2005.

[6] Marcie L. Rabin, Veena M. Narayan, Daniel Y. Kimberg, Daniel J. Casasanto, Guila Glosser, Joseph I. Tracy, Jacqueline A. French, Michael R. Sperling, and John A. Detre, "Functional mri predicts post-surgical memory following temporal lobectomy.," *Brain*, vol. 127, no. Pt 10, pp. 2286–98, 10 2004.

[7] K. J. Friston, A. P. Holmes, K. J. Worsley, J. B. Poline, C. D. Frith, R. S. J. Frackowiak, et al., "Statistical parametric maps in functional imaging: a general linear approach," *Human Brain Mapping*, vol. 2, no. 4, pp. 189–210, 1995.

[8] P. A. Yushkevich, J. A. Detre, D. Mechanic-Hamilton, M. A. Fernández-Seara, K. Z. Tang, A. Hoang, M. Korczykowski, H. Zhang, and J. C. Gee, "Hippocampus-specific fMRI group activation analysis using the continuous medial representation.," *Neuroimage*, vol. 35, no. 4, pp. 1516–30, 2 2007.

[9] Emilie Cousin, Carole Peyrin, Cédric Pichat, Laurent Lamalle, Jean-François F. Le Bas, and Monica Baciu, "Functional MRI approach for assessing hemispheric predominance of regions activated by a phonological and a semantic task.," *Eur J Radiol*, vol. 63, no. 2, pp. 274–85, 8 2007.

[10] Bérengère Aubert-Broche, Pierre Jannin, Arnaud Biraben, Anne-Marie M. Bernard, Claire Haegelen, Florence Prigent Le Jeune, and Bernard Gibaud, "Evaluation of methods to detect interhemispheric asymmetry on cerebral perfusion SPECT: application to epilepsy.," *J Nucl Med*, vol. 46, no. 4, pp. 707–13, 4 2005.